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Synthesis and Regioselective *N*-2-Functionalization of 4-Fluoro-5-aryl-1,2,3-*NH*-triazoles

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Abstract: New efficient synthesis of 4-fluoro-5-aryl-1,2,3-*NH*-triazoles was elaborated. The reaction of NaN_3 with arylsubstituted α-fluoronitroalkenes resulted in domino construction of target fluorinated triazoles. Sulfamic acid was found to be an effective promoter for this heterocyclization. It was demonstrated that subsequent functionalization of obtained triazoles proceeds highly regioselectively at the *N*-2 position. The observed regioselectivity was supported by DFT calculations.

Introduction

1,2,3-Triazoles are heterocycles of special interest. Their chemistry underwent a substantial growth during last two decades.[1] Both *NH*- and *N*-substituted 1,2,3-triazoles are shown to possess wide range of biological activities, and consequently are frequently employed in drug design (Figure 1).[2,3] Moreover, 1,2,3-triazoles are important starting compounds for the synthesis of other fundamental heterocycles, including imidazoles and pyrroles.[4] Selective functionalization of *N*-unsubstituted triazoles represents a significant problem because of a mixture of regioisomeric products is usually formed.[1a] Fluorine-containing triazoles could be a topic of special interest. Incorporation of fluorine atom is known to have a significant effect on chemical, physical and biological properties of substances. Thus, much effort has been paid to develop new synthetic methods toward fluorine-containing molecules and especially fluorinated heterocycles.[5] However, to date only one general method for the synthesis of fluoro-substituted 1,2,3-triazoles has been reported.[6,7] Click reaction of azides with 1-iodoacetylenes followed by halogen exchange afforded *N*-1-substituted 5-fluorotriazoles (Scheme 1).[6] Unfortunately, isomeric fluorotriazoles can not be prepared by this method. Currently, among fluorinated 1,2,3-triazoles only *N*-1-substituted derivatives are readily available.

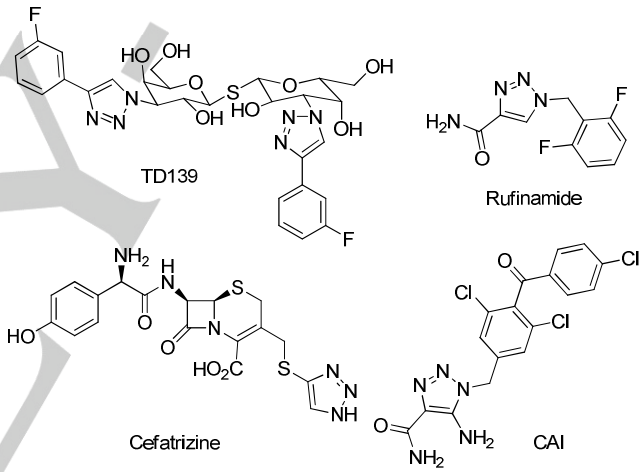
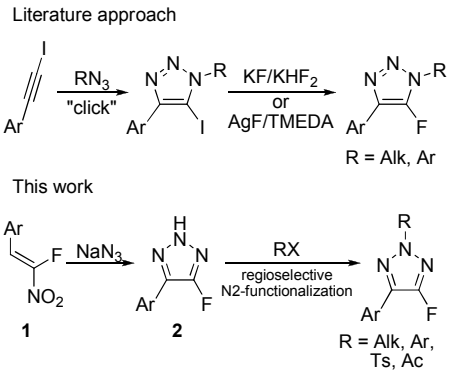


Figure 1. Some bioactive 1,2,3-triazole derivatives.



Scheme 1. Approaches toward fluoro-1,2,3-triazoles.

Recently, two procedures for the synthesis of α-fluoronitroalkenes **1** were developed.[8] We have also demonstrated their application for the preparation of various

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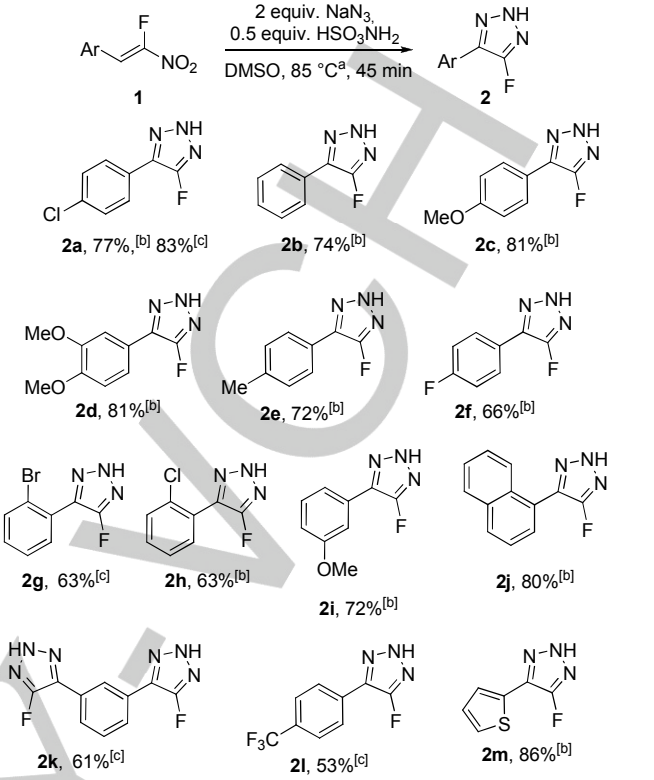
monofluorinated molecules.[8a,9] Herein we report the first synthesis of 4-fluoro-5-aryl-1,2,3-*NH*-triazoles **2** *via* the addition of sodium azide to α-fluoronitroalkenes as well as synthesis of 2-substituted 4-fluoro-1,2,3-triazoles obtained by their selective *N*-2-functionalization. Key step of our approach is nitroalkene-azide cycloaddition reaction.[10,11]

Results and Discussion

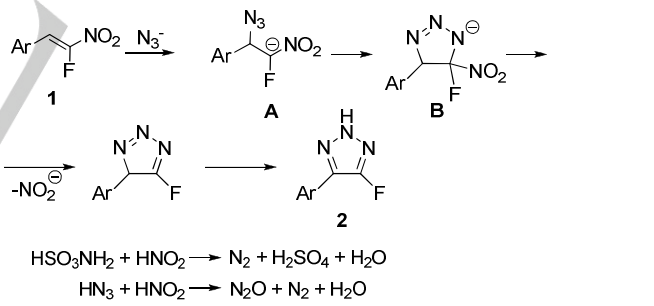
α-Fluoronitroalkene **1a** was chosen as a model substrate to find optimal conditions for the reaction with sodium azide. An influence of solvent, reagents ratio, temperature, concentration, as well as some acidic additives were studied (see Supporting Information for full optimization table). Firstly, optimization experiments showed the necessity of elevated temperatures and revealed DMSO as the appropriate solvent. Importantly, the reaction outcome showed strong dependence on the substrate concentration with higher yields achieved at lower concentrations of the reagents. To avoid large solvent waste acidic additives were tested. Finally, slow addition[10a] (during 30 min) of nitroalkene **1a** to the solution of 2 equiv. of NaN_3 and 0.5 equiv. of sulfamic acid HSO_3NH_2 in DMSO afforded triazole **2a** in 75% yield and these conditions were found optimal for subsequent experiments.

These optimized reaction conditions were spread to other α-fluoronitroalkenes **1** (Scheme 2). The procedure was found to be efficient for α-fluoronitroalkenes **1** with electron-donating or neutral groups, including methyl, methoxy and halo-substituted derivatives. Target triazoles **2** were obtained in yields up to 86%. Herewith electron-rich substrates usually gave higher yields (**2c,d,i,j,m**). However, it was demonstrated that somewhat lower yields (e.g., for **2g**, **2k**) could be increased using more dilution (0.03 M). In the case of **1l**, presence of EWG *p*-CF_3-group resulted in the moderate yield of triazole **2l**. *m*-NO_2-Substituted substrate gave low yield of the corresponding triazole and the product could not be separated from impurities. Fluoronitroalkenes **1** containing strong electron withdrawing groups such as *p*-nitrophenyl and *p*-cyanophenyl failed to give target triazoles, probably due to anionic polymerization of nitroalkene. Structures of products **2** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy and high-resolution mass-spectrometry.

Possible mechanism of the reaction includes Michael addition of azide-anion to nitroalkene **1** with subsequent ring-closure to form triazoline intermediate **B** (Scheme 3).[10a,d] Subsequent elimination of nitrite anion and proton migration furnishes target triazole **2**. Improved yields in the presence of sulfamic acid can be explained by: (a) trapping of nitrous acid to prevent some side reactions (b) suppression of polymerization of anion **A**.[10c-e]



Scheme 2. Synthesis of 4-fluoro-1,2,3-*NH*-triazoles **2**. [a] Nitroalkene was added portionally to the heated solution of NaN_3/HSO_3NH_2 for 30 min. [b] 0.1 M solution. [c] 0.03 M solution.



Scheme 3. Possible mechanism of the reaction.

According to literature data, *N*-unsubstituted 1,2,3-triazoles exist as a mixtures of tautomers having proton delocalized among all three nitrogens. The ratio of tautomers depends on structure, solvent, concentration and temperature.[12] However, according to results of X-ray diffraction analysis of triazole **2a** (Figure 2),[13] a hydrogen atom resides at the central nitrogen atom of the triazole, as additionaly supported by CN(1)N and NN(2)N angles equal to 101.78(12) and 115.98(12)°, respectively, thus making it a 2H-tautomer. In crystal, this hydrogen atoms is involved in a rather strong hydrogen bonding N(2)-H…N(1) (N…N 2.9311(17) Å, NHO 159.8(19)°) that assemble the molecules into an infinite tape. Low temperature NMR (-80 °C, THF-d_8) also did not show

noticeable duplication of ^{1}H and ^{19}F signals. Our DFT calculations also supported the strong preference of 2H-form. Moreover, 4-fluoro substituted triazole **2b** have the biggest preference of 2H-tautomer among other 4-substituted triazoles **3** (X = Cl, Br, H) (Figure 3).

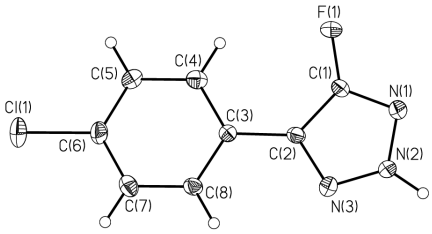


Figure 2. General view of the triazole **2a**. The non-hydrogen atoms are drawn as thermal ellipsoids at 50% probability level.

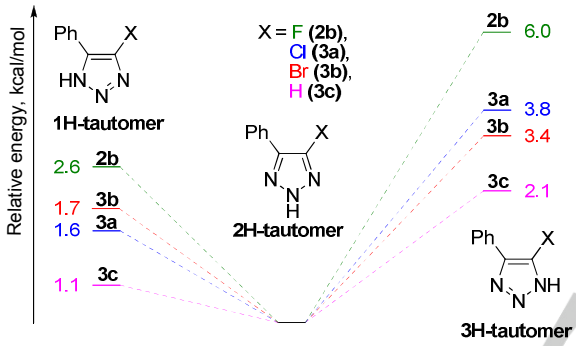
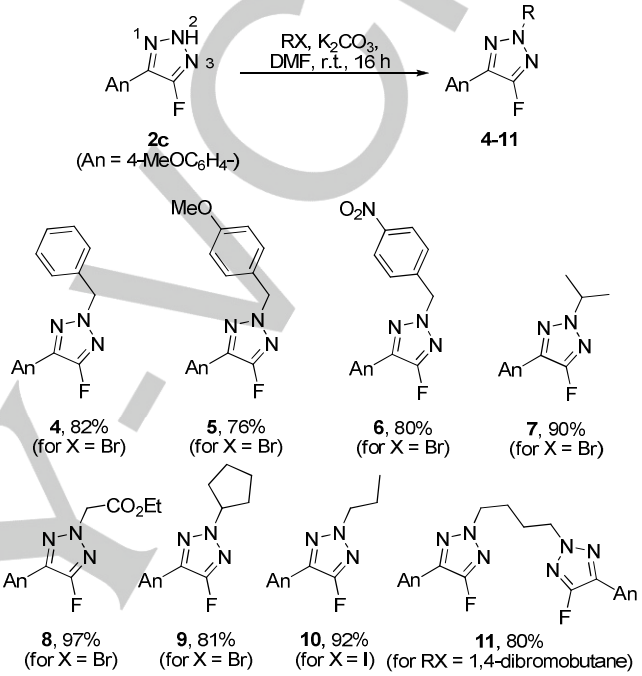


Figure 3. B3LYP/6-311+G(d,p)//PCM(DMF) relative Gibbs free energies of various 4-substituted triazoles **2b,3**.

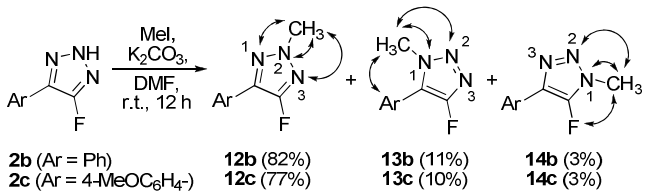
Next, functionalization of prepared fluorinated triazoles **2** was studied. Generally, *N*-functionalization (e.g., alkylation) of *NH*-1,2,3-triazoles can lead to a complex mixture of *N*-1, *N*-2 and *N*-3-substituted regioisomers in various ratios.[1a] Due to this reason *N*-1- and *N*-3-substituted triazoles are preferred to synthesize using click reactions.[1c,d] Regioselective synthesis of *N*-2-substituted triazoles is still a challenging task. Previously, good *N*-2-regioselectivity of functionalization for *N*-unsubstituted triazoles was observed usually for triazoles having sterically bulky substituents, such as bromine, iodine or aryl.[14,15] Otherwise, hydrogen-bonding interactions[16] or the use of transition metal catalysis with bulky ligands was necessary for the selective modification at the *N*-2-position.[17]

Compound **2c** was chosen as a model substrate to study *N*-functionalization of 4-fluoro substituted *NH*-triazoles. To our delight, alkylation of triazole **2c** with alkyl halides led to selective formation of *N*-2-substituted products **4-11** in 76-97% yields (Scheme 4). Moreover, the alkylation of **2c** using both primary (benzyl bromide, ethyl bromoacetate, 1,4-dibromobutane, *n*-propyl iodide) and secondary (*iso*-propyl bromide, cyclopentylbromide) alkylating reagents resulted in formation of the *N*-2-substituted isomers. Both electron donating (*p*-OMe) and electron accepting (*p*-NO_2) benzyl bromides gave *N*-2-substituted products **5** and **6** in high yields. Whereas *N*-2-substituted 4-fluoro-1,2,3-triazoles cannot be synthesized by previously reported click-reaction – halogen substitution method,[6] this regioselective alkylation might be useful for the synthesis of new *N*-2-substituted triazoles containing a fluorine atom at the position 4 of the heterocycle.



Scheme 4. *N*-2-alkylation of 4-fluoro-1,2,3-triazole **2c**.

Only in the case of small and highly active methyl iodide detectable amounts of isomeric products **13** and **14** (total 13-14%) were isolated (Scheme 5). Regiochemistry of substitution was unambiguously determined using combination of NMR experiments involving ^{1}H-^{1}H NOESY, ^{1}H-^{19}F HOESY and ^{1}H-^{15}N HMBC (see Scheme 5 and SI).[18] Thus, isomer **13** showed Me-Ar cross peak in ^{1}H-^{1}H NOESY and two ^{1}H-^{15}N HMBC interactions (Me-N1 and Me-N2). Conversely, isomer **14** showed Me-F cross peak in ^{1}H-^{19}F HOESY and two ^{1}H-^{15}N HMBC interactions (Me-N1 and Me-N2). In turn, N2-isomer **12** showed no Me-F (HOESY) and Me-Ar (NOESY), while all three possible ^{1}H-^{15}N HMBC interactions were detected. Similar NMR patterns were observed for other products **4-11**. Structure of triazole **11** was supported by X-ray analysis (Figure 4). The results of alkylation are in good agreement with DFT calculations demonstrating both thermodynamic and kinetic preference of methylation of fluorotriazolate-anions **15** at the *N*-2 position (Figure 5, also see Supporting Information).



Scheme 5. Methylation of **2**, characteristic ^{1}H-^{15}N HMBC, ^{1}H-^{1}H NOESY and ^{1}H-^{19}F HOESY interactions in products **12-14**.

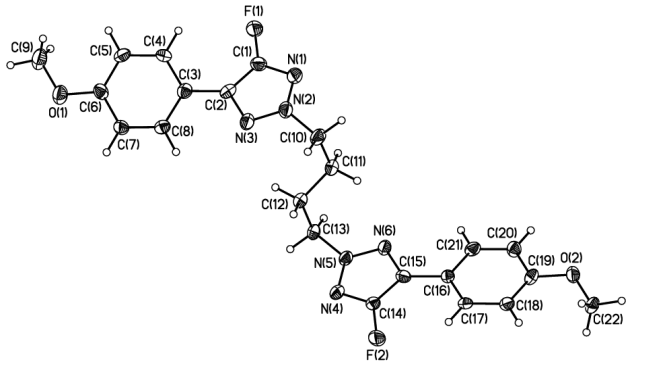


Figure 4. General view of the triazole **11**. The non-hydrogen atoms are drawn as thermal ellipsoids at 50% probability level.

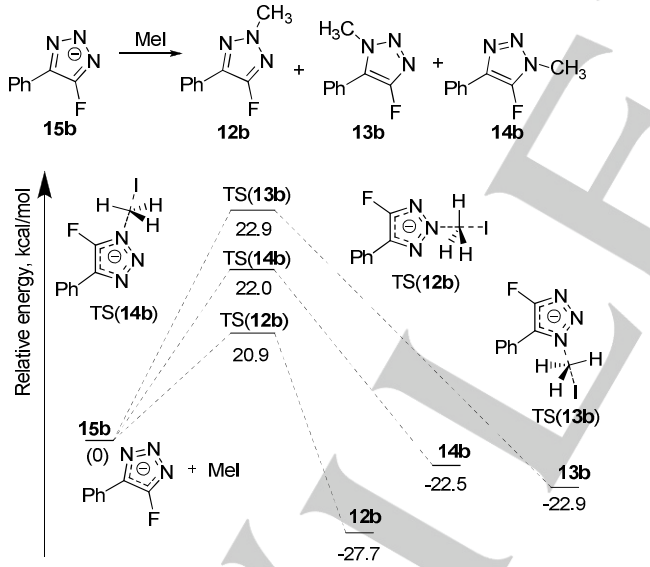
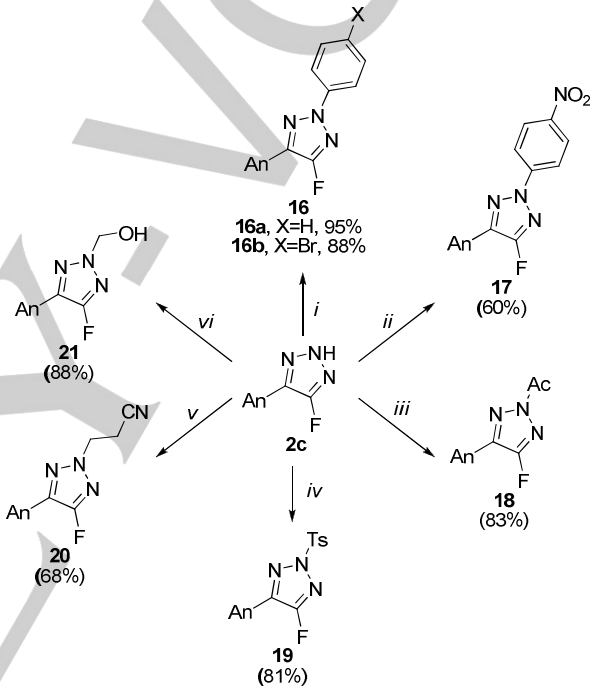


Figure 5. DFT study of methylation of fluoro-triazolate anion **15b**.

Next, other possibilities for modification of 4-fluorotriazoles **2** were demonstrated. To our delight arylation, acylation (Ac_2O), sulfonylation (TsCl), hydroxymethylation and Michael addition (H_2C=CHCN) proceeded smoothly to afford selectively *N*-2-substituted products **16-21** in high isolated yields (Scheme 6). Among different known methods for triazole arylation[15] S_NAr-substitution reaction with *p*-nitrofluorobenzene (product **17**) and Chan-Lam coupling with boronic acids (products **16**) were studied.[19] Both methods demonstrated high effectiveness for the synthesis of 2-arylated triazoles. In addition to NMR and HRMS data structures of **16b** and **18** were confirmed by X-ray analysis (Figure 6).[13] Chan-Lam coupling was performed using 10% of cupric acetate monohydrate-DMSO-oxygen system at 100°C.[20] It should be noted that *N*-2-aryl-1,2,3-triazoles are compounds of practical interest because this type of triazoles are known to possess fluorescence properties.[21] Indeed, aryltriazoles **16** were found to be fluorescent active, emitting blue light. Subsequent investigation of their fluorescent properties is currently underway.



Scheme 6. Regioselective functionalization of triazole **2c**. *i*: *p*-$XC_6H_4B(OH)_2$, 10 mol.% $Cu(OAc)_2$, O_2, DMSO, 100 °C, 2 h; *ii*: *p*-FC_6H_4NO2, K_2CO_3, DMSO, 70 °C, 1 h; *iii*: Ac_2O, NEt_3, CH_2Cl_2, r.t., 3 h; *iv*: TsCl, NEt_3, CH_2Cl_2, r.t., 40 min; *v*: CH_2=CHCN, NEt_3, DMF, r.t., 20 h; *vi*: CH_2O, H_2O, r.t., 20 h.

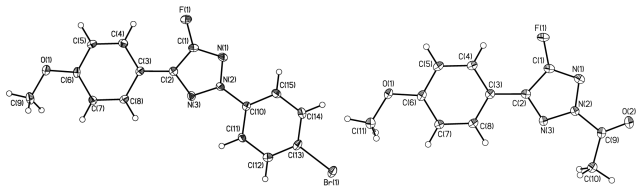


Figure 6. General views of the triazoles **16b** (left) and **18** (right). The non-hydrogen atoms are drawn as thermal ellipsoids at 50% probability level.

High regioselectivity of such modification of triazoles **2** can be explained by interplay of steric and electronic factors. *N*-1 position of triazoles **2** is hindered by bulky aryl substituent at the carbon 5 of triazole ring. On the other hand, nucleophilicity of N3

is diminished due to high electron negativity of fluorine.[22] Therefore, the combination of these factors makes attack of electrophiles more preferable at *N*-2 position. DFT calculations for model 4-fluoro-5-phenyltriazole **2b** and its anion **15b** confirmed that *N*-2 functionalization is favorable in terms of both charge and orbital control. Moreover, deprotonation of **2b** results in significant increase in HOMO-coefficient at *N*-2 leading to higher selectivity of substitution (Figure 7).

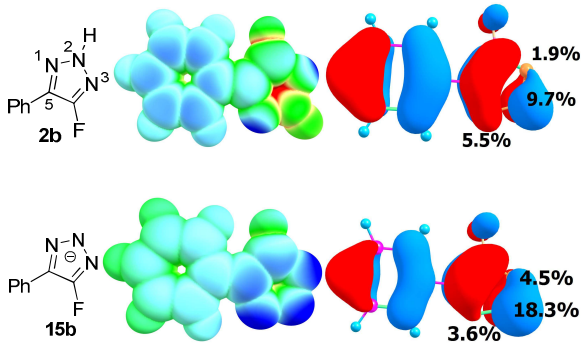


Figure 7. Electron density map and HOMO with atomic contributions at nitrogens of **2b** and its anion **15b**.

Conclusions

In conclusion, new fluorine containing heterocycles – 5-aryl-4-fluoro-1,2,3-*NH*-triazoles – were successfully synthesized from corresponding fluoronitrostyrenes and sodium azide. The possibility of their highly regioselective *N*-2 modification was demonstrated. Various synthetic methods to create new N-C bond can be used efficiently for this aim including alkylation, hydroxymethylation, acylation, Michael addition and arylation.

Experimental Section

General procedure 1. Synthesis of 4-fluoro-5-aryl-1,2,3-*NH*-triazoles 2a-2m

Caution!: Although we did not experience any accidents in our experiments, care has to be taken due to the hazardous nature of HN_3 that may be produced upon reaction of sodium azide with strong acids. Pure HN_3 is toxic and explosive, thus reactions should be performed in diluted solutions, in a well-ventilated fume hood behind a safety shield.[23a] Azide-containing water waste should be properly disposed.[23b] Sodium azide (130 mg, 2 mmol) and HSO_3NH_2 (47 mg, 0.5 mmol) were dissolved in DMSO (10 mL). Mixture was heated to 85 °C, then α-fluoronitroalkene **1a-1m** (1 mmol) (or solution of α-fluoronitroalkene **1b**, **1f** in DMSO (1 mL), if nitroalkene was liquid) was added in small portions with vigorous stirring during 30 min. Mixture was heated for additional 15 min, and poured into EtOAc/H_2O (30 / 30 mL). Aqueous layer was extacted by EtOAc (3 × 20 mL), organic layers were combined, washed with saturated NaCl solution (30 mL), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography (SiO_2, PE:EtOAc, 1:1 – 10:1). R_f(products) = 0.20-0.36 (1:1-3:1 PE:EtOAc).

4-Fluoro-5-(4-chlorophenyl)-2H-1,2,3-triazole (2a)

A) Fluorotriazole **2a** was obtained from α-fluoronitroalkene **1a** (201.5 mg, 1 mmol) following the general procedure 1. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2a** (152 mg, 77%) as slightly yellow solid. B) Fluorotriazole **2a** was obtained from α-fluoronitroalkene **1a** (280 mg, 1.39 mmol) following the general procedure 1 with the change: DMSO (46 mL) was used. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2a** (228 mg, 83%) as slightly yellow solid. R_f = 0.40 (PE/EtOAc, 3:1) (UV). m.p. 106-107 °C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 2H), 11.85 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.1 (d, ^3J(C,F) = 4.1 Hz), 127.4 (d, ^4J(C,F) = 3.5 Hz), 129.3, 130.0 (d, ^2J(C,F) = 16.0 Hz), 135.1, 159.2 (d, ^1J(C,F) = 253.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.2 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_8H_6ClFN_3$: 198.0229; Found: 198.0230. Single-crystal X-Ray diffraction data for **2a** was deposited at Cambridge Crystallographic Data Centre (CCDC-1557133).

4-Fluoro-5-phenyl-2H-1,2,3-triazole (2b)

Fluorotriazole **2b** was obtained from α-fluoronitroalkene **1b** (83.5 mg, 0.50 mmol) following the general procedure 1. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2b** (60 mg, 74%) as colorless solid. R_f = 0.33 (PE/EtOAc, 3:1) (UV). m.p. 92-94 °C (PE/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.52 (m, 3H), 7.87 (d, *J* = 7.6 Hz, 2H), 11.75 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.1, 127.6, 129.0. 130.9 (br), 159.4 (d, ^1J(C,F) = 253.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.6 (s). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_8H_6FN_3Na$: 164.0619; Found: 164.0619.

4-Fluoro-5-(4-methyloxyphenyl)-2H-1,2,3-triazole (2c)

Fluorotriazole **2c** was obtained from α-fluoronitroalkene **1c** (197 mg, 1 mmol) following the general procedure 1. Column chromatography (eluent: 3:2, PE:EtOAc) afforded **2c** (157 mg, 81%) as yellow solid. R_f = 0.55 (PE/EtOAc, 1:1) (UV). m.p. 94-95 °C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 11.9 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4, 114.5, 120.0. 127.5, 130.5 (br), 158.9 (d, ^1J(C,F) = 252.2 Hz), 160.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -145.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_9H_9FN_3O$: 194.0724; Found 194.0727.

4-Fluoro-5-(3,4-dimethyloxyphenyl)-2H-1,2,3-triazole (2d)

Fluorotriazole **2d** was obtained from α-fluoronitroalkene **1d** (76 mg, 0.335 mmol) following the general procedure 1. Column chromatography (eluent: 1:1, PE:EtOAc) afforded **2d** (61 mg, 81%) as slightly yellow solid. R_f = 0.36 (PE/EtOAc, 3:1) (UV). m.p. 207-209 °C (decomp., PhMe). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (s, 3H), 3.82 (s, 3H), 7.07 (d, 1H, *J* = 8.2 Hz), 7.28 (m, 1H), 7.30 (s, 1H), 14.8 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.9, 56.0. 109.4 (d, ^4J(C,F) = 2.0 Hz), 112.7, 118.8 (d, ^4J(C,F) = 3.8 Hz), 120.4, 127.3 (br), 149.6, 149.7, 158.7 (d, ^1J(C,F) = 246.4 Hz). ^{19}F NMR (DMSO-d_6) δ -148.4 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{10}H_{11}FN_3O_2$: 224.0830; Found: 224.0830.

4-Fluoro-5-(4-methylphenyl)-2H-1,2,3-triazole (2e)

Fluorotriazole **2e** was obtained from α-fluoronitroalkene **1e** (128 mg, 0.71 mmol) following the general procedure 1. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2e** (90 mg, 72%) as slightly yellow solid. R_f = 0.35 (PE/EtOAc, 3:1) (UV). m.p. 99-100 °C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 11.9 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 124.6,

126.0. 129.7, 130.5 (d, ^2J(C,F) = 16.8 Hz), 139.1, 159.2 (d, ^1J(C,F) = 252.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -145.0 (s). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_9H_8FN_3Na$: 200.0594; Found: 200.0592.

4-Fluoro-5-(4-fluorophenyl)-2H-1,2,3-triazole (2f)

Fluorotriazole **2f** was obtained from α-fluoronitroalkene **1f** (154.5 mg, 0.84 mmol) following the general procedure 1. Column chromatography (eluent: 7:1, PE:EtOAc) afforded **2f** (100 mg, 66%) as slightly yellow solid. R_f = 0.35 (PE /EtOAc, 3:1) (UV). m.p. 131-133 °C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.37 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.73-7.81 (t, *J* = 9.0 Hz, 2H), 14.7 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.6 (d, ^2J*(C,F)* = 21.9 Hz), 124.6, 127.0 (d, ^2J*(C,F)* = 17.0 Hz), 128.2 (dd, *J(C,F)* = 8.5, 3.4 Hz), 158.8 (d, ^1J*(C,F)* = 247.2 Hz), 162.5 (d, ^1J*(C,F)* = 246.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.6 (tt, J_{HF} = 8.9, 5.4 Hz), -148.2 (s). HRMS (ESI) *m/z*: $[M - H]^-$ Calcd. for $C_8H_4F_2N_3$: 180.0368; Found 180.0362.

4-Fluoro-5-(2-bromophenyl)-2H-1,2,3-triazole (2g)

Fluorotriazole **2g** was obtained from α-fluoronitroalkene **1g** (122 mg, 0.50 mmol) following the general procedure 1 with the change: DMSO (17 mL) was used. Column chromatography (eluent: 5:1, PE:EtOAc) afforded **2g** (76 mg, 63%) as slightly yellow solid. R_f = 0.30 (PE/EtOAc, 3:1) (UV). m.p. 83-84 °C (PhMe). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.40-7.57 (m, 3H), 7.80 (*d*, J = 7.9 Hz, 1H), 15.07 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 122.9, 128.1, 128.5, 128.9 (d, ^2J(C,F) = 13.7 Hz), 131.8, 132.5, 133.6, 158.7 (d, ^1J(C,F) = 256.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -145.4 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_8H_6{}^{79}BrFN_3$: 241.9724; Found: 241.9730.

4-Fluoro-5-(2-chlorophenyl)-2H-1,2,3-triazole (2h)

Fluorotriazole **2h** was obtained from α-fluoronitroalkene **1h** (83 mg, 0.412 mmol) following the general procedure 1. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2h** (51 mg, 63%) as colorless solid. R_f = 0.29 (PE/EtOAc, 3:1) (UV). m.p. 75-76 °C (PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.46 (m, 2H), 7.47-7.66 (m, 2H), 12.0 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.5, 127.4, 130.7, 131.0. 131.5, 132.3, 133.5, 159.6 (d, ^1J(C,F) = 252.7 Hz, C-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -141.9 (s). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_8H_5ClFN_3Na$: 220.0048; Found: 220.0053.

4-Fluoro-5-(3-methyloxyphenyl)-2H-1,2,3-triazole (2i)

Fluorotriazole **2i** was obtained from α-fluoronitroalkene **1i** (123 mg, 0.62 mmol) following the general procedure 1. Column chromatography (eluent: 4:1, PE:EtOAc) afforded **2i** (87 mg, 72%) as colorless solid. R_f = 0.26 (PE/EtOAc, 3:1) (UV). m.p. 76-77 °C (PhMe). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H), 6.96 (ddd, *J* = 8.0. 2.4, 1.0 Hz, 1H), 7.32-7.49 (m, 3H), 11.57 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 111.3, 115.0. 118.6, 128.9, 130.0. 130.5 (d, ^2J(C,F) = 13.0 Hz), 159.4 (d, ^1J(C,F) = 252.7 Hz), 160.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.4 (s). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_9H_8FN_3ONa$: 216.0544; Found: 216.0538.

4-Fluoro-5-(1-naphthalenyl)-2H-1,2,3-triazole (2j)

Fluorotriazole **2j** was obtained from α-fluoronitroalkene **1j** (61 mg, 0.298 mmol) following the general procedure 1. Column chromatography (eluent: 5:1, PE:EtOAc) afforded **2j** (48 mg, 80%) as colorless solid. R_f = 0.31 (PE/EtOAc, 3:1) (UV). m.p. 103-104 °C (PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51-7.63 (m, 3H), 7.70 (d, *J* = 7.1 Hz, 1H), 7.94 (m, 2H), 8.22 (m, 1H) 12.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.0. 125.1, 125.3, 126.4, 127.1, 128.1 (d, ^4J(C,F) = 2.2 Hz), 128.7, 130.1, 131.0. 133.9, 159.9 (d, ^1J(C,F) = 252.6 Hz, C-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.8 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{12}H_9FN_3$: 214.0775; Found: 214.0778.

5,5'-Benzenediylbis-(4-fluoro-2H-1,2,3-triazole) (2k)

Fluorotriazole **2k** was obtained from α-fluoronitroalkene **1k** (300 mg, 1.17 mmol) following the general procedure 1 with the change: NaN_3 (305 mg, 4 equiv., 4.69 mmol), HSO_3NH_2 (110 mg, 1 equiv., 1.17 mmol) in DMSO (39 mL) was used. Column chromatography (eluent: 1:1, PE/EtOAc) afforded **2k** (177 mg, 61%) as slightly yellow solid. R_f = 0.30 (PE/EtOAc, 1:1) (UV). m.p. 87-89 °C (PE). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.61 (t, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 8.14 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 122.7, 126.1, 127.4 (br), 129.0. 130.6, 159.1 (d, ^1J(C,F) = 247.7 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ = -147.2 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{10}H_7F_2N_6$: 249.0695, found: 249.0697.

4-Fluoro-5-(4-(trifluoromethyl)phenyl)-2H-1,2,3-triazole (2l)

Fluorotriazole **2l** was obtained from α-fluoronitroalkene **1l** (115 mg, 0.49 mmol) following the general procedure 1 with the change: DMSO (16 mL) was used. Column chromatography (eluent: 3:1, PE:EtOAc) afforded **2l** (59.5 mg, 53%) as colorless oil, which solidified upon storage in the fridge. R_f = 0.31 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.87 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.5 (q, ^1J(C,F) = 272.0 Hz), 126.5, 126.6, 126.9, 129.1 (q, ^2J(C,F) = 32.0 Hz), 132.3 (d, ^3J(C,F) = 3.4 Hz), 159.4 (d, ^1J(C,F) = 248.7 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.3 (s, 3F), -146.4 (s, 1F). HRMS (ESI) *m/z*: $[M - H]^-$ Calcd. for $C_9H_4F_4N_3$: 230.0336. found: 230.0342.

4-Fluoro-5-(2-thienyl)-2H-1,2,3-triazole (2m)

Fluorotriazole **2m** was obtained from α-fluoronitroalkene **1m** (18.0 mg, 0.10 mmol) following the general procedure 1. Column chromatography (eluent: 7:3, PE:EtOAc) afforded **2m** (15.2 mg, 86%) as orange oil. R_f = 0.40 (PE/EtOAc, 7:3) (UV). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.20 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.43 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.68 (dd, *J* = 5.1, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 124.2 (br), 125.6 (d, *J*(C,F) = 2.9 Hz), 126.8, 128.1, 128.7 (d, *J*(C,F) = 4.1 Hz), 157.3 (d, ^1J(C,F) = 247.8 Hz). ^{19}F NMR (282 MHz, DMSO-d_6): δ = --148.3 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_6H_4FN_3S$: 170.0183. found: 170.0186.

General procedure 2. Synthesis of *N*-2-alkyl-4-fluoro-1,2,3-triazoles 4-12.

Fluorotriazole **2c** (0.3 mmol, 58 mg) and alkyl halide (0.32 mmol, 1.05 equiv.) were dissolved in DMF (1 mL), then K_2CO_3 (0.45 mmol, 1.5 equiv, 41 mg) was added. Mixture was stirred at room temperature for 16 hours, and extracted with EtOAc/H_2O (20/20 mL). Aqueous layer was washed with EtOAc (2 × 15 mL), organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography (SiO_2, PE:EtOAc, 1:1 – 10:1). R_f (products) = 0.30-0.61 (3:1, PE:EtOAc).

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(phenylmethyl)-2H-1,2,3-triazole (4)

Alkyltriazole **4** was obtained from *NH*-triazole **2c** (21.5 mg) and benzyl bromide following the general procedure 2. Column chromatography (eluent: 7:1, PE:EtOAc) afforded **4** (26 mg, 82%) as slightly yellow solid.

R_f = 0.44 (PE/EtOAc, 3:1) (UV). m.p. 60-61 °C (PE/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 5.45 (s, 2H, CH_2), 6.98 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.34-7.38 (m, 5H, Ph), 7.76 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 59.3, 114.3, 120.9 (d, ^3J(C,F) = 4.3 Hz), 127.3 (d, ^4J(C,F) = 3.4 Hz), 128.1, 128.5, 128.8, 130.5 (d, ^2J(C,F) = 15.0 Hz), 134.8, 158.4 (d, ^1J(C,F) = 253.1 Hz), 159.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -143.7 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 231 (N-C), 301 and 330 (2 × C=N). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_{16}H_{14}FN_3ONa$: 284.1194; Found: 284.1186.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-{[4-(methyloxy)phenyl]methyl}-2H-1,2,3-triazole (5)

Alkyltriazole **5** was obtained from *NH*-triazole **2c** (42.8 mg, 0.22 mmol) and *p*-methoxybenzyl bromide (46 mg, 0.23 mmol) following the general procedure 2. Column chromatography (eluent: 8:1, PE:EtOAc) afforded **5** (52.6 mg, 76%) as slightly yellow solid. R_f = 0.37 (PE/EtOAc, 3:1) (UV). m.p. 67-68 °C (PE/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 5.38 (s, 2H, CH_2), 6.90 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.34 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (2×O<u>Me</u>), 58.9, 114.1, 114.2, 120.9 (d, ^3J(C,F) = 4.4 Hz), 126.9, 127.3 (d, ^4J(C,F) = 3.4 Hz), 129.6, 130.2 (d, ^2J(C,F) = 15.0 Hz), 158.3 (d, ^1J(C,F) = 253.0 Hz), 159.8 (2×<u>C</u>-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -143.9 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 233 (N-C), 301 and 328 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{17}H_{17}FN_3O_2$: 314.1299; Found: 314.1301.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-[(4-nitrophenyl)methyl]-2H-1,2,3-triazole (6)

Alkyltriazole **6** was obtained from *NH*-triazole **2c** (45.1 mg, 0.23 mmol) and *p*-nitrobenzyl bromide (52.9 mg, 0.25 mmol) following the general procedure 2. Column chromatography (eluent: 8:1, PE:EtOAc) afforded **6** (61.3 mg, 80%) as yellow solid. R_f = 0.31 (PE/EtOAc, 3:1) (UV). m.p. 98-99 °C (PE/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 5.54 (s, 2H, CH_2), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{An}), 7.49 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.74 (d, *J* = 8.7 Hz, 2H, CH_{An}), 8.22 (d, *J* = 8.8 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 58.2, 114.3, 120.3 (d, ^3J(C,F) = 4.3 Hz), 124.0, 127.4 (d, ^4J(C,F) = 3.4 Hz), 128.8, 131.3 (d, ^2J(C,F) = 15.0 Hz), 141.7, 148.0, 158.5 (d, ^1J(C,F) = 254.4 Hz), 160.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.8 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 227 (N-C), 302 and 330 (2 × C=N), 369 (NO_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{16}H_{14}FN_4O_3$: 329.1044; Found: 329.1049.

4-Fluoro-2-(1-methylethyl)-5-[4-(methyloxy)phenyl]-2H-1,2,3-triazole (7)

Alkyltriazole **7** was obtained from *NH*-triazole **2c** (34 mg) and *iso*-propyl bromide following the general procedure 2. Column chromatography (eluent: 5:1, PE:EtOAc) afforded **7** (37 mg, 90%) as colourless liquid, which solidifies upon storage in the fridge. R_f = 0.53 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 6.7 Hz, 6H, CH-<u>Me</u>), 3.85 (s, 3H, OMe), 4.68 (hept d, *J* = 6.7, 0.9 Hz, 1H, C<u>H</u>-Me), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.76 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0. 55.3, 57.9, 114.3, 121.3 (d, ^3J(C,F) = 4.4 Hz), 127.2 (d, ^4J(C,F) = 3.4 Hz), 129.1 (d, ^2J(C,F) = 15.2 Hz), 157.8 (d, ^1J(C,F) = 251.5 Hz), 159.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.8 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 243. Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{12}H_{15}FN_3O$: 236.1194; Found: 236.1194.

Ethyl (4-fluoro-5-[4-(methyloxy)phenyl]-2H-1,2,3-triazol-2-yl)acetate (8)

Alkyltriazole **8** was obtained from *NH*-triazole **2c** (20 mg) and ethyl bromo acetate following the general procedure 2. Column chromatography (eluent: 5:1, PE:EtOAc) afforded **8** (28 mg, 97%) as slightly yellow oil which solidifies upon storage in the fridge. R_f = 0.40 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3H, CH_2-<u>Me</u>), 3.86 (s, 3H, OMe), 4.27 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.07 (s, 2 H, N-CH_2), 6.98 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.76 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 55.3, 56.0. 62.2, 114.3, 120.5 (d, ^3J(C,F) = 4.2 Hz), 127.5 (d, ^4J(C,F) = 3.3 Hz), 131.7 (d, ^2J(C,F) = 15.1 Hz), 158.6 (d, ^1J(C,F) = 254.1 Hz), 160.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.9. ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 218 (N-C), 303 and 331 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{13}H_{15}FN_3O_3$: 280.1092; Found: 280.1082.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(cyclopentyl)-2H-1,2,3-triazole (9)

Alkyltriazole **9** was obtained from *NH*-triazole **2c** (26.5 mg) and cyclopentyl bromide following the general procedure 2. Column chromatography (eluent: 8:1, PE:EtOAc) afforded **9** (29 mg, 81%) as colorless liquid, which solidifies upon storage in the fridge. R_f = 0.61 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64-2.03 (m, 4H, cyclopentyl), 2.07-2.32 (m, 4H, cyclopentyl), 3.83 (s, 3H, OMe), 4.86 (quint, 1H, N-C<u>H</u>), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 32.5, 55.3, 66.7, 114.2, 121.3 (d, ^3J(C,F) = 4.4 Hz), 127.2 (d, ^4J(C,F) = 3.3 Hz), 129.2 (d, ^2J(C,F) = 15.1 Hz), 157.8 (d, ^1J(C,F) = 251.6 Hz), 159.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.6 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 241 (N-C), 297 and 327 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{14}H_{17}FN_3O$: 262.1350; Found: 262.1350.

4-Fluoro-2-propyl-5-[4-(methyloxy)phenyl]-2H-1,2,3-triazole (10)

Alkyltriazole **10** was obtained from *NH*-triazole **2c** (46.6 mg, 0.24) and *n*-propyl iodide (45 mg, 0.26 mmol) following the general procedure 2. Column chromatography (eluent: 8:1, PE:EtOAc) afforded **10** (51.8 mg, 92%) as colourless liquid, which solidifies upon storage in the fridge. R_f = 0.44 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3H, CH_2-<u>Me</u>), 1.99 (m, *J* = 7.2 Hz, 2H, C<u>H</u>$_2$-Me), 3.85 (s, 3H, OMe), 4.24 (t, *J* = 7.2 Hz, 2H, C<u>H</u>$_2$-N), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0, 22.9, 55.3, 57.2, 114.3, 121.1 (d, ^3J(C,F) = 4.4 Hz), 127.2 (d, ^4J(C,F) = 3.4 Hz), 129.6 (d, ^2J(C,F) = 15.0 Hz), 158.0 (d, ^1J(C,F) = 251.7 Hz), 159.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.9 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 232 (N-C), 300 and 328 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{12}H_{15}FN_3O$: 236.1194; Found: 236.1196.

2,2'-Butane-1,4-diylbis{4-fluoro-5-[4-(methyloxy)phenyl]-2H-1,2,3-triazole} (11)

Alkyltriazole **11** was obtained from *NH*-triazole **2c** (30.5 mg) following the general procedure 2 using 2.0 equiv of 2b and 1.0 equiv. of 1,4-dibromobutane. Column chromatography (eluent: 5:1, PE:EtOAc) afforded **11** (28 mg, 80%) as colorless solid. R_f = 0.24 (PE/EtOAc, 3:1) (UV). m.p. 86-87 °C (PE/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (d, *J* = 5.9 Hz, 4H, N-CH_2-C<u>H</u>$_2$), 3.85 (s, 6H, OMe), 4.36 (d, *J* = 5.9 Hz, 4H, N-CH_2), 6.96 (d, 4H, *J* = 8.8 Hz, CH_{Ar}), 7.73 (d, 4H, *J* = 8.8 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 54.6, 55.3, 114.3, 120.9 (d, ^3J(C,F) = 4.4 Hz), 127.3 (d, ^4J(C,F) = 3.3 Hz), 130.0 (d, ^2J(C,F) = 15.0 Hz), 158.0 (d, ^1J(C,F) = 252.5 Hz), 159.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ

= -144.3 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 230 (N-C), 300 and 329 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{23}F_2N_6O_2$: 441.1845; Found: 441.1849. Single-crystal X-Ray diffraction data for **11** was deposited at Cambridge Crystallographic Data Centre (CCDC-1557134).

4-Fluoro-2-methyl-5-phenyl-2H-1,2,3-triazole (12b), 4-Fluoro-1-methyl-5-phenyl-1H-1,2,3-triazole (13b) and 5-Fluoro-1-methyl-4-phenyl-1H-1,2,3-triazole (14b)

Methylation of **2b** (60 mg, 0.37 mmol) with methyl iodide (55 mg, 0.39 mmol) following general procedure 2 and purification by column chromatography (SiO_2, PE:EtOAc, 9:1) afforded product **12b** (53.3 mg, 82%) and mixture of two other regioisomers **13b** and **14b** (9.4 mg, 14%) with ratio **13b:14b** = 3:1 (determined by NMR) as colorless oils. Data for **12b**: R_f = 0.45 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (s, 3H, Me), 7.34-7.48 (m, 3H, CH_{Ar}), 7.81 (d, *J* = 7.6 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.4, 125.8 (d, ^4J(C,F) = 3.6 Hz), 128.3 (d, ^3J(C,F) = 4.2 Hz), 128.4, 128.9, 130.1 (d, ^2J(C,F) = 14.6 Hz), 158.4 (d, ^1J(C,F) = 252.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -143.8 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 222 (N-C), 303 and 331 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_9H_9FN_3$: 178.0775; Found: 178.0782. Data for **13b**: R_f = 0.20 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (s, 3H, Me), 7.43-7.58 (m, 5H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1, 125.3 (d, ^3J(C,F) = 3.3 Hz), 119.9 (d, ^2J(C,F) = 29.2 Hz), 128.6 (d, ^4J(C,F) = 1.4 Hz), 129.3, 129.7, 158.4 (d, ^1J(C,F) = 245.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -145.1 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 232 (N-C), 343 (C=N). Other signals are not visible due to low intensity. Data for **14b**: R_f = 0.20 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.01 (d, *J* = 1.3 Hz, 3H, Me), 7.35-7.58 (m, 3H, CH_{Ar}), 7.85 (d, *J* = 7.3 Hz, 2H, CH_{Ar}). ^{13}C NMR (57 MHz, $CDCl_3$): δ = 33.2, 124.5 (d, ^3J(C,F) = 4.2 Hz), 128.1, 128.9. Other signals are not visible due to low intensity and/or overlapping. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -152.8 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 219 (N-C), 342 (C=N). Other signals are not visible due to low intensity. HRMS (**13b**+**14b** mixture) (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_9H_9FN_3$: 178.0775; Found: 178.0773.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(methyl)-2H-1,2,3-triazole (12c), 4-Fluoro-5-[4-(methyloxy)phenyl]-3-(methyl)-3H-1,2,3-triazole (13c) and 4-Fluoro-5-[4-(methyloxy)phenyl]-1-(methyl)-1H-1,2,3-triazole (14c)

Methylation of **2c** (72 mg, 0.373 mmol) with methyl iodide following general procedure 2 and purification by column chromatography (SiO_2, PE:EtOAc, 3:1) afforded product **12c** (59 mg, 76%) and mixture of two other regioisomers **13c** and **14c** (10 mg, 13%) with ratio **13c:14c** = 4:1 (determined by NMR). Data for **12c**: R_f = 0.43 (PE/EtOAc, 3:1) (UV). m.p. 59-60 °C (PE/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, OMe), 4.08 (s, 3H, Me), 6.98 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.74 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.3, 55.3, 114.3, 120.9 (d, ^3J(C,F) = 4.3 Hz), 127.2 (d, ^4J(C,F) = 3.4 Hz), 130.1 (d, ^2J(C,F) = 14.8 Hz), 158.0 (d, ^1J(C,F) = 251.8 Hz), 159.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.8 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 220 (N-C), 302 and 330 (2 × C=N). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{10}H_{11}FN_3O$: 208.0881; Found: 208.0883. Data for **13c**: R_f = 0.16 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H, OMe), 4.03 (s, 3H, Me), 7.05 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.37 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9, 55.4, 114.8, 116.5 (d, ^3J(C,F) = 4.1 Hz), 119.8 (d, ^2J(C,F) = 29.8 Hz), 130.0 (d, ^4J(C,F) = 1.1 Hz), 158.2 (d, ^1J(C,F) = 244.7 Hz), 160.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -145.6 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 232 (N-C), 341 (C=N). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{10}H_{11}FN_3O$: 208.0881; Found: 208.0885. Data for **14c**: R_f = 0.16 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 3.99 (d, *J* = 1.2 Hz, 3H, Me), 6.99 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.77 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.1, 55.3, 114.3, 121.3 (d, ^3J(C,F) = 4.7 Hz), 126.6 (d, ^4J(C,F) = 3.1 Hz), 158.3 (d, ^1J(C,F) = 251.4 Hz), 160.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -154.1 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 219 (N-C), 340 (C=N). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{10}H_{11}FN_3O$: 208.0881; Found: 208.0883.

General procedure 3. Synthesis of *N*-2-aryl-4-fluoro-1,2,3-triazoles 16.

In 10 mL round-bottomed flask fluorotriazole **2c** (0.3 mmol, 58 mg), boronic acid (0.39 mmol, 1.3 eq) and copper(II) acetate monohydrate (0.03 mmol, 0.1 equiv, 6 mg) were dissolved in 3 mL of DMSO. Flask was connected to balloon with O_2, and the mixture was heated to 100°C. After 2-3 h of stirring (TLC monitoring) mixture was cooled to room temperature and extracted with EtOAc/H_2O (20/20 mL). Aqueous layer was washed with EtOAc (2 × 15 mL), organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography (SiO_2, PE:EtOAc, 10:1).

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(phenyl)-2H-1,2,3-triazole (16a)

Aryltriazole **16a** was obtained from *NH*-triazole **2c** (38 mg) and benzeneboronic acid following the general procedure 3. Column chromatography (eluent: 10:1, PE:EtOAc) afforded 1**6a** (51 mg, 95%) as white solid. R_f = 0.60 (PE/EtOAc, 3:1) (UV). m.p. 94-95 °C (PE/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3H, OMe), 7.02 (d, *J* = 8.7 Hz, 2H, CH_{An}), 7.34 (m, 1H, *p*-CH_{Ph}), 7.49 (m, 2H, *m*-CH_{Ph}), 7.88 (d, *J* = 8.7 Hz, 2H, CH_{An}), 8.02 (m, 2H, *o*-CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 114.4, 117.9, 120.5 (d, ^3J(C,F) = 4.3 Hz), 127.2, 127.6 (d, ^4J(C,F) = 3.4 Hz), 129.3, 131.9 (d, ^2J(C,F) = 15.3 Hz), 139.6, 159.4 (d, ^1J(C,F) = 255.1 Hz), 160.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.0 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 234 (N-C). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{15}H_{13}FN_3O$: 270.1037; Found: 270.1028.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(4-bromophenyl)-2H-1,2,3-triazole (16b)

Aryltriazole **16b** was obtained from *NH*-triazole **2c** (58 mg, 0.30 mmol) following the general procedure 3. Column chromatography (eluent: 10:1, PE:EtOAc) afforded **16b** (92 mg, 88%) as white solid. R_f = 0.58 (PE/EtOAc, 3:1) (UV). m.p. 138-139 °C (PE/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H, OMe), 7.01 (d, *J* = 8.7 Hz, 2H, CH_{An}), 7.60 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 7.86 (d, *J* = 8.7 Hz, 2H, CH_{An}), 7.90 (d, *J* = 8.9 Hz, 2H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 114.4, 119.4, 120.2 (d, ^3J(C,F) = 4.2 Hz), 120.7, 127.7 (d, ^4J(C,F) = 3.3 Hz), 132.4, 132.5, 138.5, 159.5 (d, ^1J(C,F) = 256.1 Hz), 160.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -141.1 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 232 (N-C). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd. for $C_{15}H_{11}{}^{79}BrFN_3ONa$: 348.0142; Found: 348.0144. Single-crystal X-Ray diffraction data for **16b** was deposited at Cambridge Crystallographic Data Centre (CCDC-1557135).

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(4-nitrophenyl)-2H-1,2,3-triazole (17)

Fluorotriazole **2c** (20.7 mg, 0.11 mmol) was dissolved in 1.1 mL of DMSO, then *p*-fluoronitrobenzene (17 mg, 1.1 equiv., 0.12 mmol) and

K_2CO_3 (22 mg, 1.5 equiv., 0.16 mmol) were added. Mixture was heated to 70 °C and stirred for 2 hours, then cooled to room temperature, poured into EtOAc/H_2O (20/20 mL). Aqueous layer was washed with EtOAc (2 × 15 mL), organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure. Column chromatography (SiO_2, PE:EtOAc, 10:1) afforded aryltriazole **17** (20 mg, 60%) as yellow crystalline solid. R_f = 0.48 (PE/EtOAc, 3:1) (UV). m.p. 183-185 °C (PE/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OMe), 7.03 (d, *J* = 8.7 Hz, 2H, CH_{An}), 7.89 (d, *J* = 8.7 Hz, 2H, CH_{An}), 8.17 (d, *J* = 9.3 Hz, 2H, CH_{Ar}), 8.37 (d, *J* = 9.3 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4, 114.5, 117.9, 119.5 (d, ^3J(C,F) = 4.0 Hz), 125.2, 127.2 (d, ^4J(C,F) = 3.4 Hz), 134.4 (d, ^2J(C,F) = 15.5 Hz), 143.4, 146.1, 160.3 (d, ^1J(C,F) = 259.2 Hz), 160.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -138.6 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): 229 (N-C), 368 (NO_2). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: [M + H^+] Calcd. for $C_{15}H_{12}FN_4O_3$: 315.0888; Found: 315.0881.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-acetyl)-2H-1,2,3-triazole (18)

Fluorotriazole **2c** (52 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (1.3 mL), then Ac_2O (33 mg, 1.2 equiv, 0.32 mmol) and Et_3N (33 mg, 1.3 equiv, 0.32 mmol) were added. Mixture was stirred at room temperature for 3 hours, diluted with CH_2Cl_2 to 20 mL and washed with water (20 mL). Aqueous layer was washed with 10 mL of CH_2Cl_2, organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Recrystallization from PE:EtOAc (5:1) afforded product **18** as yellow needle-like crystals (52.5 mg, 83 %). R_f = 0.42 (PE/EtOAc, 3:1) (UV). m.p. 135-137 °C (PE/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (s, 3H, Me), 3.86 (s, 3H, OMe), 7.00 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.89 (d, *J* = 8.7 Hz, 2H, CH_{Ar}).^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 55.3, 114.6, 118.7 (d, ^3J(C,F) = 4.1 Hz), 128.4 (d, ^4J(C,F) = 3.1 Hz), 137.0 (d, ^2J(C,F) = 16.9 Hz), 160.4 (d, ^1J(C,F) = 265.4 Hz), 161.3, 165.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -134.6 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 251 (N-C). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: [M + H]$^+$ Calcd. for $C_{11}H_{11}FN_3O_2$: 236.0830; Found: 236.0829. Single-crystal X-Ray diffraction data for **18** was deposited at Cambridge Crystallographic Data Centre (CCDC-1557136).

4-Fluoro-5-[4-(methyloxy)phenyl]-2-[(4-methylphenyl)sulfonyl)]-2H-1,2,3-triazole (19)

Fluorotriazole **2c** (40.5 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (0.53 mL), then TsCl (44 mg, 1.1 equiv, 0.23 mmol) and Et_3N (32 mg, 1.5 equiv, 0.32 mmol) were added. Mixture was stirred at room temperature for 40 min, diluted with CH_2Cl_2 to 20 mL and washed with water (20 mL). Aqueous layer was washed with 10 mL of CH_2Cl_2, organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Column chromatography (SiO_2, PE:EtOAc, 10:1) afforded product **19** as white solid (59 mg, 81 %). R_f = 0.47 (PE/EtOAc, 3:1) (UV). m.p. 137-138 °C (PE/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H, Me), 3.85 (s, 3H, OMe), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.36 (d, *J* = 8.3 Hz, 2H, CH_{Ts}), 7.81 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.96 (d, *J* = 8.3 Hz, 2H, CH_{Ts}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (Me), 55.3 (OMe), 114.5 (CH_{Ar}), 118.6 (d, ^3J(C,F) = 4.1 Hz, C_{Ar}), 128.3 (d, ^4J(C,F) = 3.5 Hz, CH_{Ar}), 128.7 (CH_{Ts}), 130.2 (CH_{Ts}), 132.6 (C_{Ts}), 137.2 (d, ^2J(C,F) = 17.0 Hz, C=N), 146.8 (C_{Ts}), 160.1 (d, ^1J(C,F) = 267.0 Hz, C=N), 161.2 (C_{Ar}). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -134.3 (s). HRMS (ESI) *m/z*: [M + H]$^+$ Calcd. for $C_{16}H_{15}FN_3O_3S$: 348.0813; Found: 348.0808.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(2-cyanoethyl)-2H-1,2,3-triazole (20)

Fluorotriazole **2c** (26.7 mg, 0.14 mmol) was dissolved in DMF (0.7 mL), then acrylonitrile (10 mg, 1.3 equiv, 0.18 mmol) and Et_3N (21 mg, 1.5 equiv, 0.21 mmol) were added. Mixture was stirred at room temperature for 20 hours, then poured into EtOAc/H_2O (20/20 mL). Aqueous layer was washed by EtOAc (3 × 10 mL), organic layers were combined, washed with saturated NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. Column chromatography (SiO_2, PE:EtOAc, 10:1) afforded product **20** (23 mg, 68 %) as colorless liquid, which solidifies in the fridge. R_f = 0.13 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.04 (t, *J* = 6.9 Hz, 2H, CH_2-CN), 3.86 (s, 3H, OMe), 4.59 (t, *J* = 6.9 Hz, 2H, N-C$\underline{H}_2$), 6.98 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.5 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 50.5, 55.3, 114.4, 116.1, 120.2 (d, ^3J(C,F) = 4.3 Hz), 127.5 (d, ^4J(C,F) = 3.4 Hz), 131.6 (d, ^2J(C,F) = 15.0 Hz), 158.4 (d, ^1J(C,F) = 254.8 Hz), 160.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.5 (s). ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 223 (N-C), 252 (C≡N), 301 and 328 (2 × N=C). HRMS (ESI) *m/z*: [M + H]$^+$ Calcd. for $C_{12}H_{12}FN_4O$: 247.0990; Found: 247.0988.

4-Fluoro-5-[4-(methyloxy)phenyl]-2-(hydroxymethyl)-2H-1,2,3-triazole (21)

Fluorotriazole **2c** (39.5 mg, 0.205 mmol) was suspended with stirring in the 37% aqueous formaldehyde solution (10 equiv., 166 mg, 0.15 mL). Reaction mixture was stirred overnight, quenched with water (10 mL), and product was extracted with EtOAc (2 × 20 mL). The organic layer was evaporated. Recrystallization from PE:EtOAc (1:1) afforded 40 mg (88%) of product **21** as slightly yellow crystals. R_f = 0.10 (PE/EtOAc, 5:1) (UV). m.p. 81-82 °C (PE/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (br t, *J* = 7.7 Hz, 1H, OH), 3.86 (s, 3H, OMe), 5.67 (d, *J* = 7.7 Hz, 2H, CH_2), 6.99 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.76 (d, *J* = 8.7 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ. 55.3, 77.1, 114.4, 120.3 (d, ^3J(C,F) = 4.3 Hz), 127.5 (d, ^4J(C,F) = 3.4 Hz), 132.1 (d, ^2J(C,F) = 15.5 Hz), 158.8 (d, ^1J(C,F) = 255.7 Hz), 160.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.2. ^{15}N NMR (30 MHz, $CDCl_3$, from {^{1}H–^{15}N}HMBC): δ = 299 and 328 (2 × N=C). Other signals are not visible due to low intensity. HRMS (ESI) *m/z*: [M + H]$^+$ Calcd. for $C_{10}H_{11}FN_3O_2$: 224.0830; Found: 224.0833.

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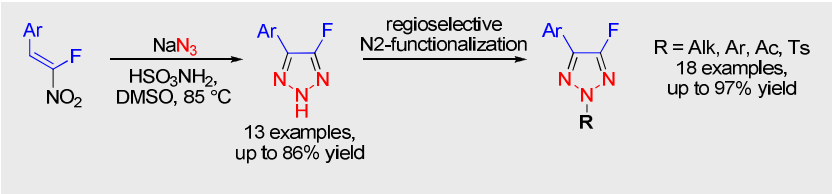

Efficient synthesis of 4-fluoro-5-aryl-1,2,3-*NH*-triazoles was elaborated using reaction of NaN_3 with arylsubstituted α-fluoronitroalkenes. Subsequent functionalization of obtained triazoles proceeds highly regioselectively at the *N*-2 position. The observed regioselectivity was supported by DFT calculations.

Fluorinated heterocycles

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Synthesis and Regioselective *N*-2-Functionalization of 4-Fluoro-5-aryl-1,2,3-*NH*-triazoles